PCRM PHYSICIANS COMMITTEE FOR RESPONSIBLE MEDICINE
5100 WISCONSIN AVENUE, NW • SUITE 400
WASHINGTON, DC 20016
(202) 686-2210 FAX: (202) 686-2216
WWW.PCRM.ORG

July 18, 2001

The Honorable Christine Todd Whitman
Administrator
U.S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Ave., N.W.
Washington, DC 20460

Subject: Comments on Test Plan for Terpenoid Primary Alcohols and Related Esters

Dear Administrator Whitman:

The following comments on the test plan for the Terpenoid Primary Alcohols and Related Esters (TPARE) are submitted on behalf of the Physicians Committee for Responsible Medicine, People for the Ethical Treatment of Animals, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These health, animal protection, and environmental organizations have a combined membership of more than nine million Americans.

The Flavor and Fragrance High Production Volume Consortia have developed a well-constructed category and have presented robust summaries that adequately address each health endpoint of the SIDS battery and all but one ecotoxicity endpoint. Any further testing on animals would not contribute to the understanding of the toxicity of TPARE. We recommend that no further testing on animals be conducted and that the proposed fish toxicity tests be deleted. Our greatest concern is that this category was not combined with other categories sponsored by the consortia, such as the Terpenoid Tertiary Alcohol and Related Esters, to form an even larger terpenoid group, as was done for the GRAS (Generally Recognized as Safe) certification of these compounds (Adams 1996, Adams 1998). An analysis of a larger category would provide an even greater understanding of the structure activity relationships of these similar substances.

1. The Terpenoid Primary Alcohol and Related Ester (TPARE) chemical category is appropriate, well understood, and defensible.

The TPARE category presented by the Flavor and Fragrance Consortia is an example of a logically circumscribed group of chemicals, whose production and metabolism in plants and animals is well understood. All these compounds have very similar structures, based on 3,7-dimethy-6-octenol, with two of the compounds (Nerol and Geraniol) being enantiomers of each other (they are compositionally and functionally identical but are mirror images of each other). Clearly, this group meets all criteria in the EPA's guidance for applying structure activity relationships.

The analysis of the group is sophisticated and underscored by a thorough understanding of the biochemical properties of these compounds. This type of category analysis has been applied in internationally accepted safety analyses for decades. In addition, there is a well-developed body of knowledge of the toxicokinetics of these substances, including their hydrolysis in the gastrointestinal tract, gastric absorption rates, and behavior in the liver and other organs. The biochemical, toxicokinetic, structural, functional, and exposure data all indicate that it is entirely appropriate to include these substances in a single group.

Despite the overwhelming evidence supporting the category formation, we remain concerned that the EPA may reject this category. The EPA has disregarded the biochemical, structural, and toxicokinetic information presented in previously proposed HPV test plans and rejected seven of the nine proposed categories, violating its own October 1999 agreement with industry representatives, environmental groups, and animal protection organizations that outlined minimal animal welfare concerns. This agreement declares, "Participants shall maximize the use of scientifically appropriate categories of related chemicals and structure activity relationships."

2. Existing data demonstrate the low toxicity of these compounds.

Overall, the compounds in the TPARE group have a very low toxicity. Many of the compounds in the group already occur naturally in common foods, and some are endogenous to mammals. All compounds in the group are classified as GRAS by the Food and Drug Administration. Observations of human populations that directly consume millions of pounds of these products in fruits and vegetables indicate that they are not particularly toxic.

We applaud the consortia's evaluation of existing *in vitro* genotoxicity data in their development of their test plan. The importance of *in vitro* data has been downplayed, missing, or ignored in other test plans submitted under the HPV program.

3. The TPARE test plan demonstrates a major flaw of the HPV program: the exclusion of human exposure assessment.

The TPARE test plan underscores out one of the fundamental flaws of the HPV program: excluding exposure information from the analysis. Since biogenic production of these compounds exceeds industrial production by orders of magnitude, the industrial emissions of these chemicals will be negligible compared to the natural, background concentrations. Additionally, exposure to these compounds from the consumption of plants is more than an order of magnitude greater than exposure due to the ingestion of manufactured forms of these compounds. Because the HPV program has no mechanism to include this critical exposure information, more irrelevant animal testing is being proposed.

4. Any aquatic toxicity testing on these chemicals is inappropriate and unnecessary.

We recommend that the aquatic tests on fish be deleted from the test plan. As described in previous test plan comments to the Consortia, data on aquatic toxicity can be collected by using quantitative structure activity relationships or *in vitro* tests. *In vitro* tests with the protozoan *tetrahymena* are frequently used as a measure of aquatic toxicity in ecological risk assessments. We have requested a meeting with the EPA to discuss how to incorporate these alternative, non-animal methods into the HPV program.

Additionally, the consortia have already provided ECOSAR aquatic toxicity estimates, which may overestimate the toxicity, but still indicate a generally low aquatic toxicity. The ECOSAR estimates provide an adequate, conservative evaluation of aquatic toxicological hazard consistent with the scope of the HPV program.

Thank you for the opportunity to comment and I look forward to your response. I can be reached via telephone at (202) 686-2210, ext. 302, or via e-mail at <ncardello@pcrm.org>. Correspondence should be sent to my attention at the following address: PCRM, 5100 Wisconsin Ave., NW., Suite 400, Washington, DC 20016.

Sincerely,

Nicole Cardello, M.H.S.

cc:
The Honorable Sherwood Boehlert
The Honorable Ken Calvert
The Honorable Jerry Costello
The Honorable Robert C. Smith

References:

Adams TB, Greer DB, Doull J, Munro IC, Newberne P, Portoghese PS, Smith RL, Wagner BM, Weil CS, Woods LA, and Ford RA. The FEMA GRAS Assessment of Lactones Used as Flavour Ingredients. *Food and Chemical Toxicology* 1998 36:249-78.

Adams TB, Hallagan JB, Putnam JM, Gierke TL, Doull J, Munro IC, Newberne P, Portoghese PS, Smith RL, Wagner BM, Weil CS, Woods LA, and Ford RA. The FEMA GRAS Assessment of Alicyclic Substances Used as Flavour Ingredients. *Food and Chemical Toxicology* 1996 34:763-828.